Chlorpyrifos and Neurodevelopmental Effects: Overview of the Columbia Study

Decades of research indicates that chlorpyrifos is only toxic at exposures that are high enough to inhibit acetylcholinesterase (AChE) activity in the brain. The range of exposures experienced by children and pregnant women are far lower than those that can cause AChE inhibition.

Even so, several relatively recent epidemiology studies have evaluated prenatal chlorpyrifos exposure and birth outcomes (*e.g.*, infant body weight or head circumference) and neurodevelopmental (*e.g.*, mental and psychomotor) testing results. These studies have found weak and inconsistent associations.

These studies have been critically reviewed several times over the last several years (*e.g.*, Reiss *et al.*, 2015; Edwards *et al.*, 2013; Prueitt *et al.*, 2011; Gradient, 2015). The US EPA Office of Pesticide Programs (OPP) is particularly focused on the Columbia Center for Children's Environmental Health Mothers and Newborn Study (the Columbia study) and has been specifically considering analyses by Dr. Rauh and colleagues published in 2006 (Rauh *et al.*, 2006) and 2011 (Rauh *et al.*, 2011) for its re-evaluation of chlorpyrifos. These studies reported associations between low chlorpyrifos levels *in utero* and lower IQ scores and increased behavioral problems at 3 to 7 years of age. This contradicts the long-standing, strong evidence from toxicology studies demonstrating that these exposure levels do not have neurotoxic effects.

The Columbia study has many strengths compared to other epidemiology studies of chlorpyrifos, but it also has many limitations, many of which have been acknowledged by US EPA and its Scientific Advisory Panel (SAP) (US EPA, 2012). Based on concerns over these limitations, in 2012, the SAP requested additional data and analyses from the Columbia study researchers to evaluate various limitations and then strengthen the reliability of the findings for risk assessment, but the researchers did not comply. Issues related to these studies include:

- These studies relied on only one chlorpyrifos measurement from umbilical cord blood for each child. Using this one measurement, it is not possible to estimate the actual chlorpyrifos exposure experienced during gestation or early childhood.
- Over 40% of children had chlorpyrifos levels that were below the limit of detection (LOD), and over 80% were below the level of validation. To deal with measurements below the LOD, investigators used a statistical approach to estimate the unknown measurements, but this greatly reduced the accuracy of the results.
- 12% of children did not have any cord blood chlorpyrifos measurements, so levels in maternal blood were used as a surrogate measurement. This has similar issues as described in the previous point.
- Children had many other known exposures and lifestyle factors that could have contributed to neurodevelopmental effects that were not accounted for. Although the Columbia investigators attempted to account for some of these factors, it was not possible to fully account for all of them.
- In the 2006 study, the authors stated: "In preliminary analyses, we found no indication of either a linear or nonlinear dose-response relationship between chlorpyrifos levels and developmental outcomes." Associations were only reported when the data were manipulated in a specific way.
- Studies at Mount Sinai Hospital and the University of California (UC) at Berkeley do not confirm the results reported by the Columbia University researchers.

- There is no established biological mode of action to explain the potential neurodevelopmental effects reported. The animal data indicate that dose levels that cause adverse neurodevelopmental outcomes only occur at exposures that inhibit AChE in pregnant rats or offspring. A few subjects in the UC Berkeley study may have had chlorpyrifos concentrations near the lowest estimate for 10% red blood cell (RBC) AChE inhibition. All other study subjects had chlorpyrifos levels that were well below all estimates for RBC AChE inhibition.

We also note that OPP has developed guidelines for evaluating potential measurement error in epidemiology studies for use in risk assessment, but did not adhere to these guidelines for assessing measurement error in epidemiology studies of chlorpyrifos and neurodevelopmental outcomes. Unresolved uncertainties about measurement error in the Columbia study could be addressed with additional analyses of original data, and preliminary quantitative bias analyses of available summary data demonstrate that positive findings in the Columbia study could be explained by exposure or outcome misclassification.

In conclusion, all of the chlorpyrifos epidemiology studies have been reviewed by multiple parties on several occasions over the last decade, including the SAP, and several issues have been brought up repeatedly, but have never been sufficiently addressed by US EPA. Collectively, these studies are not robust enough to change the weight of evidence based on animal toxicity and mechanistic studies.

References

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